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ORIGINAL PAPER

The 'two global flash' mfERG in high and normal tension primary open-angle glaucoma

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Abstract
Purpose To analyse the sensitivity of the '2 global flash' multifocal electroretinogram (mfERG) to detect glaucomatous dysfunction in normal tension (NTG) and high tension primary open angle glaucoma (POAG) patients.
Methods MfERGs were recorded from 20 NTG and 20 POAG patients and compared to those of 20 controls. The mfERG array consisted of 103 hexagons. Each m-sequence step started with a focal flash that could be either dark or light (m-sequence: 2^13, L_{max}: 200 cd/m^2, L_{min}: 1 cd/m^2), followed by two global flashes (L_{max}: 200 cd/m^2) at an interval of ~26 ms. Focal scalar products (SP) were calculated using focal templates derived from the control recordings (VERIS 4.8). We analyzed 5 response averages (central 7.5 degrees and 4 adjoining quadrants) of the response to the focal flash, the direct component at 10–40 ms (DC) and the following two components induced by the effects of the preceding focal flash on the response to the global flashes at 40–70 ms (IC-1) and at 70–100 ms (IC-2).
Results Both NTG and POAG patients differed from controls in the IC-1 response to the superior quadrants, and POAG patients also differed from controls in the centre. The most sensitive parameter was the IC-1 of the superior temporal quadrant with an area under the ROC curve of 0.82 for POAG and 0.79 for NTG. The DC and the IC-2 did not differ significantly between the groups. When all five response averages of the IC-1 were taken into consideration 90% of the NTG patients and 85% of the POAG patients were correctly classified as abnormal while 80% of the control subjects were correctly classified as normal.
Conclusions This stimulus sequence holds promise for the diagnosis of early functional changes in POAG. A new finding is that both NTG, as well as POAG can be differentiated from control subjects.

Keywords mfERG · Global flash · Glaucoma · POAG · Normal tension glaucoma

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Introduction

Open angle glaucoma, a leading cause of blindness worldwide [1], affects at least 1.7% of the population over 40 years of age in industrial countries [2]. In POAG an increasing loss of ganglion cell fibers results in a progressive optic

atrophy with an increased cup/disc ratio and an irreversible visual field loss [3]. In an attempt to detect early glaucomatous dysfunction, the mfERG has been studied as a possible diagnostic tool for the past decade. In experimental glaucoma, nerve fiber cell damage induced in the primate results in a marked reduction of amplitude in the mfERG [4–6].

In humans, initial studies that describe changes in the mfERG secondary to glaucoma show only a small reduction in amplitude and an increase in latencies [7–10] in POAG patients when compared to a control group. However, changes in stimulation parameters have lead to an increased sensitivity of the mfERG to detect glaucomatous dysfunction. These changes have primarily focused on enhancing nonlinear contributions to the mfERG, in particular a response component, the optic nerve head component (ONHC), whose propagation time correlates well with the length of the ganglion nerve fibers and thus seems dependent on the nerve fiber layer [11–16]. In the primate, the naso-temporal asymmetry thought to be caused by this component is diminished following intravitreal administration of Tetrodotoxin, which blocks amacrine and ganglion cells [16]. The ONHC appears to be diminished in glaucoma [15, 17]. Bearse et al. have shown that the ONHC asymptotes in amplitude at a contrast of about 60% whereas the retinal component (RC) shows a linear relationship with contrast [18]. Thus low contrast recordings were thought to be more sensitive to retinal dysfunction in patients with open angle glaucoma (OAG) as reducing the stimulus contrast to 50% would enhance the relative contribution of the inner retina. While this was the case, sensitivity did not increase enough to detect individual patients as having POAG [7, 19, 20].

With an increase in the stimulus base interval, a small induced response component resulting from the response to the following stimulus in the m-sequence cycle becomes apparent. At a stimulus base interval of ~54 ms there is no overlap between the induced component and the m sequence response. Under these conditions, oscillatory potentials become apparent in the induced component [21] and the sensitivity to detect NTG increases to about 85% [22].

Adaptive mechanisms can be enhanced by interposing bright global flashes into the stimulation sequence, as suggested by Sutter et al. [23]. When global flashes are introduced into the stimulus sequence, the mfERG sensitivity to detect retinal dysfunction in glaucoma increases to 50% with the use of 3 global flashes [24] and to about 75% with a specificity of 83% with the use of a single global flash [25]. Also, in the area of a laser induced focal ganglion cell fiber layer defect in the primate, a mfERG with one global flash showed fewer and smaller high frequency oscillations, especially in the response to the global flash but also to the focal flash [26]. These changes affected high frequency components as well as low frequency components where P2 and N2 were reduced in amplitude and increased in latency [26].

In the present study we examine the sensitivity of a mfERG stimulus with two global flashes to detect glaucomatous dysfunction in NTG and POAG patients.

Methods

Subjects

MfERG recordings were obtained from 20 patients with NTG, 20 patients with POAG and compared to a control group of 20 normal subjects. The tenets of the Declaration of Helsinki were adhered to. The study was approved by the institutional review board of the University of Basel. Informed consent was obtained from patients and subjects after explanation of the nature and possible consequences of the study.

Inclusion criteria for glaucoma patients were a cup disc ratio of at least 0.5 as measured with the HRT (Heidelberg Retina Tomograph, Heidelberg Engineering, Heidelberg, Germany), localized thinning of the neuro-retinal rim of the optic disc, and the presence of a glaucomatous visual field defect. For POAG patients the highest measured IOP was >21 mmHG, while for the NTG patients this had to be less than 22 mmHg.

Exclusion criteria were the presence of other ocular or systemic diseases, such as diabetes mellitus or hypertension as well as refractive errors exceeding 6 diopters of hyperopia or

myopia. The right eye of each subject was included unless it did not fulfill the inclusion criteria or met any of the exclusion criteria. In this case, the left eye was included, if it fulfilled the eligibility criteria.

MfERG recording

For mfERG recording, patients were adapted to ambient room light for 30 minutes. Prior to recording, the pupil was maximally dilated (Tropicamide 0.5%, Phenylephrin 1%) and the cornea was anesthesized (Proxymetacain Hydrochlorid). Electrical responses were recorded monoculary via a bipolar Burian-Allan contact lens electrode (Hansen Ophthalmic Development Labs, Iowa City, IA), that was wetted with a drop of synthetic carbomer (Thilo-Tears SE^R). The other eye was occluded during the recording. The ground electrode was placed on the forehead. Subjects were refracted for best visual acuity at 40 cm. The distance between the subject and the screen was adjusted to compensate for changes in stimulus size induced by the refractive lens.

During recording, the central 50 degrees of the retina were stimulated with a Veris scientific 4.8 (Visual Evoked response Imaging System, VERIS EDI, San Mateo, California). The stimulus array consisted of 103 hexagons displayed on a monochrome monitor. The stimulus hexagons were scaled with eccentricity in order to take into account the retinal cone distribution and thus to achieve approximately equal focal response signals in the controls [27].

Figure 1 depicts the stimulus sequence used: Hexagons flickered between black and white according to an m-sequence of 2^13 (frame rate: 75 Hz). Each m-sequence step started with a focal flash that could be either light or dark (L_{max}: 200 cd/m^2, L_{min}: ≤1 cd/m^2), (M), followed by two global flashes (F, L_{max}: 200 cd/m^2). A dark frame (B, L_{max}: ≤1 cd/m^2) separated each flash in the sequence. Thus one stimulus base interval consisted of the following sequence: MBFBFB, with a stimulus base interval of ~80 ms and a contrast of 99%. The background was set at 50 cd/m^2. Retinal signals were amplified (100 000) and bandpass filtered at 10–300 Hz. The total recording time of 10 min 55 sec duration was divided into 32 segments. Segments with contaminated signals were discarded and re-recorded. The artifact rejection technique, incorporated in the software, was applied twice [27]. Spatial filtering was not used.

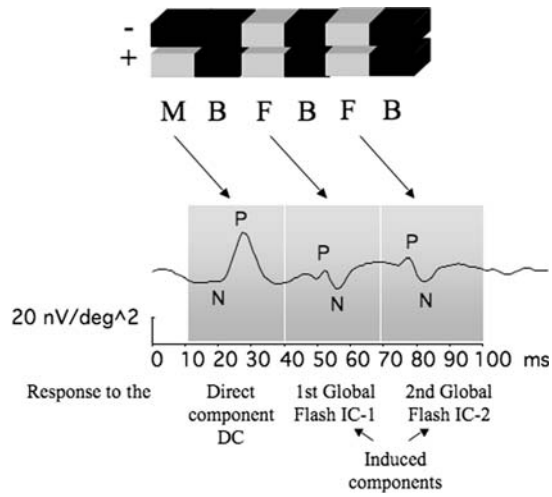

Fig. 1 Figure 1 depicts the stimulus sequence of the mfERG (top) and an example of the resulting retinal response elicited (below). Each stimulus started with a focal flash that could be either light or dark (L_{max}: 200 cd/m^2, L_{min}: 1 cd/m^2), followed by two global flashes (F, L_{max}: 200 cd/m^2) at an interval of ~26 ms. A dark frame (B, L_{max}: ≤1 cd/m^2) separated each step in the stimulus sequence. The three epochs analyzed are highlighted: the response to the focal flash at 10–40 ms (direct component, DC) and the following two components induced by the global flashes at 40–70 ms (IC-1) and at 70–100 ms (IC-2)

Response analysis

The mfERG first order response component is calculated by adding the focal mean response to a stimulus base interval starting with a light m-sequence stimulus and subtracting those starting with a dark m-sequence stimulus (Fig. 1). Therefore a response to global flashes (full-screen flashes) will only occur if they are influenced differently by the response to the preceding focal flash, which is the only stimulus frame that is not constant in the individual stimulus base intervals. Thus the presence of a response to a global flash demonstrates the presence of retinal adaptation which may be presumed to be of inner retinal origin. In addition, it has been suggested to

represent influences of lateral interactions. [23, 24, 28–30]

Figure 1 shows the three epochs of the first order response component that were analyzed: the response to the focal stimulus, found at 10–40 ms (direct component, DC) and the following two components induced by the effects of the focal stimulus on the following global flashes at 40–70 ms (induced component 1, IC-1) and at 70–100 ms (induced component 2, IC-2). The focal scalar product (SP), that is the cross product of the focal waveform and its template, was analyzed for each location and for each of the three epoch lengths (DC, IC-1, IC-2). The corresponding focal templates were derived from the 20 control recordings for each of the three epoch lengths (DC, IC-1, IC-2).

Figure 2 shows the areas over which the focal SP were averaged to form these response averages for the central 7.5 degrees (C) and the four adjoining quadrants (field view): ST: superior temporal; SN: superior nasal, IN: inferior nasal and IT: inferior temporal. For analysis of the five group averages, a repeat measure ANOVA was performed, taking into account the effects of location and age.

Results

Neither age nor visual acuity differed between the three groups studied. Mean age was 53.9 (SD 13.1) years in the control group, 56.6 (SD 8.1) years in the NTG group and 61.0 (SD 10.7) years in the POAG group (ANOVA $P = 0.126$). Snellen visual acuity was ≥0.8 in all participants. At the time of the study, IOP was under 21 mmHG in all patients. Mean IOP was 11.7 (SD 2) mmHg in the control group, 13.5 (SD 1.8) mmHg in the NTG group and 14.4 (SD 3.5) mmHg in the POAG group. Mean cup-disc-ratio was 0.33 (SD 0.06) in the control group, 0.65 (SD 0.11) in the NTG group and 0.61 (SD 0.14) in the POAG group. Mean MD was 5.25 (SD 3.4) dB in the NTG group and 5.94 (SD 3.05) dB in the POAG group. The control group differed from the NTG and POAG groups in IOP and cup-disc-ratio, but the NTG and the POAG groups did not differ significantly in IOP, cup-disc-ratio or MD.

Figure 3 shows a trace array from the right eye of a control subject over the entire epoch analyzed, 10–100 ms. The responses show a large naso-temporal asymmetry. When small nasal and small temporal response averages were analyzed (Fig. 4), it became apparent that the naso-temporal asymmetry observed was mainly due to a larger amplitude in the response average from the nasal field, in particular of the DC, but also of the IC-1 response. This naso-temporal asymmetry was seen in the control subjects and also persisted in the NTG and POAG patients. When all three response components were analyzed, considering the effect of location and age, no significant differences were found between the groups in

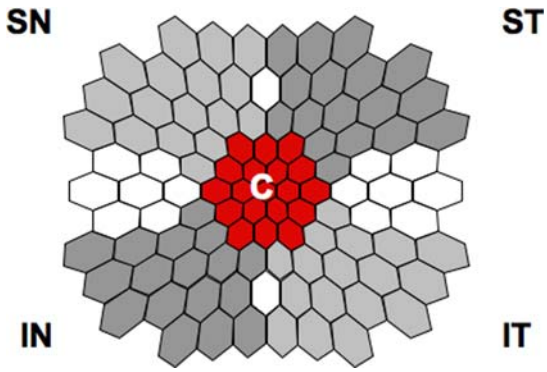

Fig. 2 Figure 2 shows the areas over which the focal SP were averaged to form response averages for the central 7 degrees (C) and the four adjoining quadrants: ST: superior temporal; SN: superior nasal, IN: inferior nasal and IT: inferior temporal

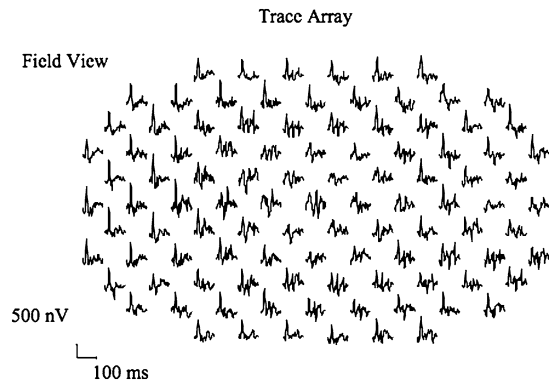

Fig. 3 Figure 3 shows a trace array of the right eye of a control over the entire epoch analyzed, 10–100 ms. The responses show a large naso-temporal asymmetry

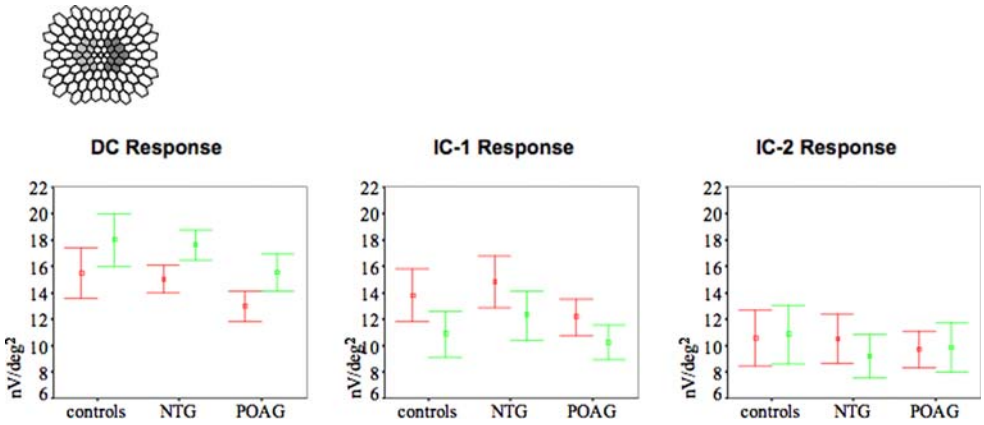

Fig. 4 Figure 4 (top left) shows the responses that were averaged to form a small nasal and a small temporal response average (field view). The plots to the right show the mean peak (P) to trough (N) amplitudes for the three response components (M, IC-1 and IC-2) shown in Fig. 1. The error bar depicts ±1 SEM. For each group, the left column depicts the temporal response average, the right column depicts the nasal response average

either amplitude or latency. When we attempted to average larger areas, the naso-temporal asymmetry resulted in a smearing out of peaks and troughs, preventing reliable peak to trough measurements. We therefore calculated focal scalar products for each epoch length analyzed as described in the method section. These focal scalar products were then averaged to form five response averages (Fig. 2).

Figure 5 shows the mean of each response average for the DC (a), the IC-1 (b) and the IC-2 (c). The error bars depict the standard error of the mean. Neither the DC (Fig. 5a), nor the response to the second global flash, the IC-2 (Fig. 5c), differed significantly between the groups. This held true for all response averages examined.

The IC-1 (Fig. 5b), the response induced by the first global flash, differed significantly between the subject groups ($P = 0.003$). There was also a significant difference in the location effect between groups $P = 0.003$. Surprisingly, this difference did not seem related to a naso-temporal asymmetry, but occurred in the superior and central fields (Table 1). In the superior fields both, the NTG and the POAG patients were significantly lower in amplitude than the control subjects ($P < 0.02$, multivariate ANOVA, Sidak). In the central response average, only POAG patients had significantly smaller IC-1 amplitudes than the control patients ($P = 0.003$). In the inferior quadrants POAG and NTG patients did not differ from the control group. There was no significant difference between POAG and NTG patients.

Figure 6 shows the distribution of the mean defect for each of the visual field quadrants (G2 program, Octopus 101, Haag-Streit AG). While on average the MD was higher in the superior fields, it did not differ significantly between quadrants. Also, the MD of the four quadrants did not correlate significantly with the age adjusted log-mfERG response of IC-1.

The area under the receiver operating characteristics (ROC) curve is a measure of the ability of a parameter to differentiate between patients and controls. Table 2 shows the area under the ROC curve for the IC-1 for each of the group averages examined. Figure 7 depicts ROC curves for the IC-1 of the superior temporal quadrant where POAG patients differed most from the controls. Here, for NTG patients, the area under the ROC curve was 0.79 and for POAG it was 0.82, which is significantly better than chance ($P \leq 0.02$). With a cutoff value of 2.5 nV/deg^2, 80% of the NTG patients and 75% of the POAG patients were correctly classified as abnormal while 80% of the control subjects were correctly classified as normal. Table 2b contains the information on sensitivity and specificity for

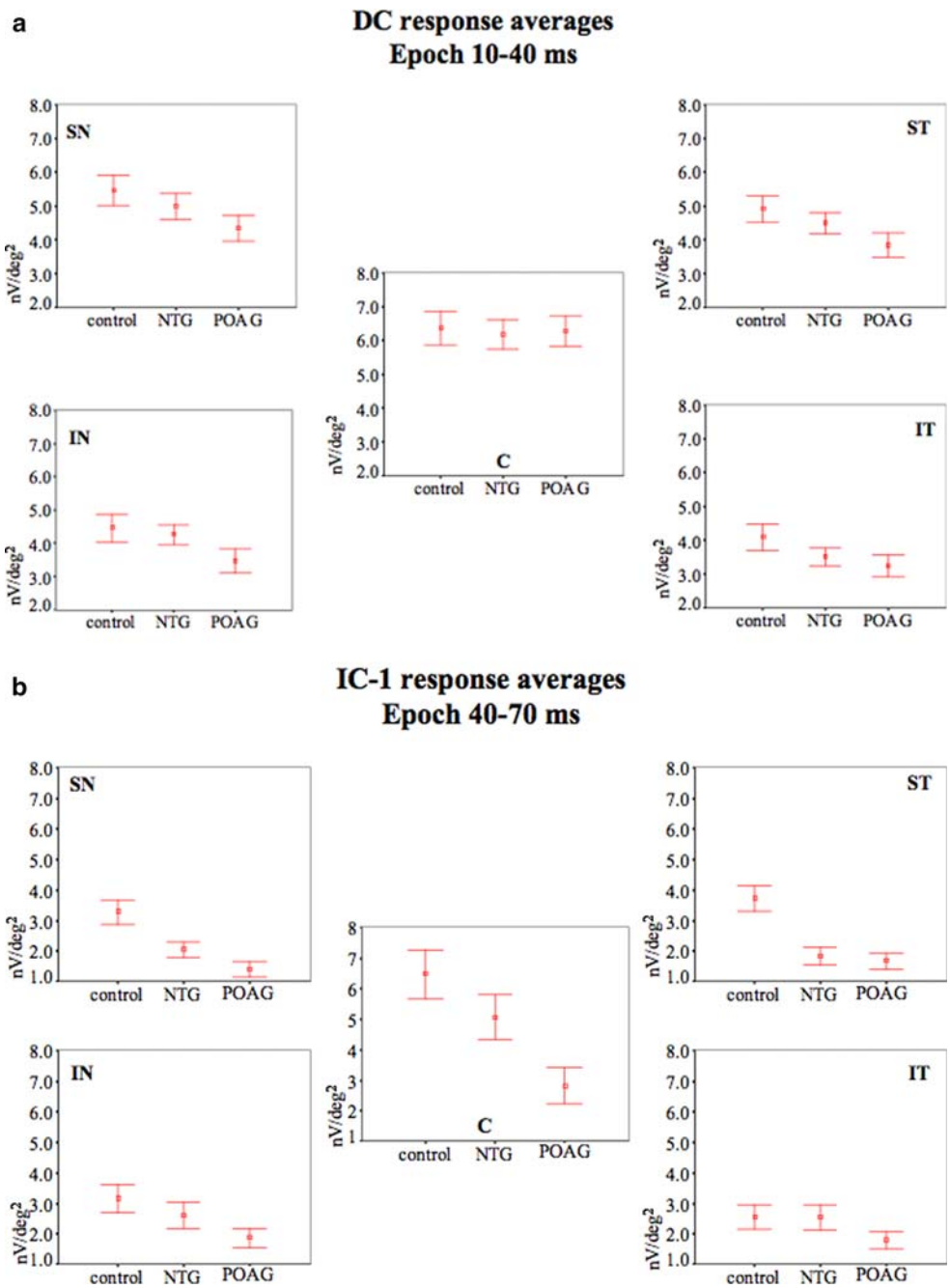

Fig. 5 depicts the mean of each response average (groups are shown in Fig. 3) for the DC (**a**), the IC-1 (**b**) and the IC-2 (**c**). The error bars depict ± 1standard error of the mean

all the response averages analyzed. Individual subjects' or patients' responses may be affected differently in the various response averages analyzed. When all five response averages of the IC-1 were taken into consideration, and using the cutoff values depicted in Table 2 b, 90% of the NTG patients and 85% of the POAG patients were correctly classified as abnormal while 80% of the control subjects were correctly classified as normal.

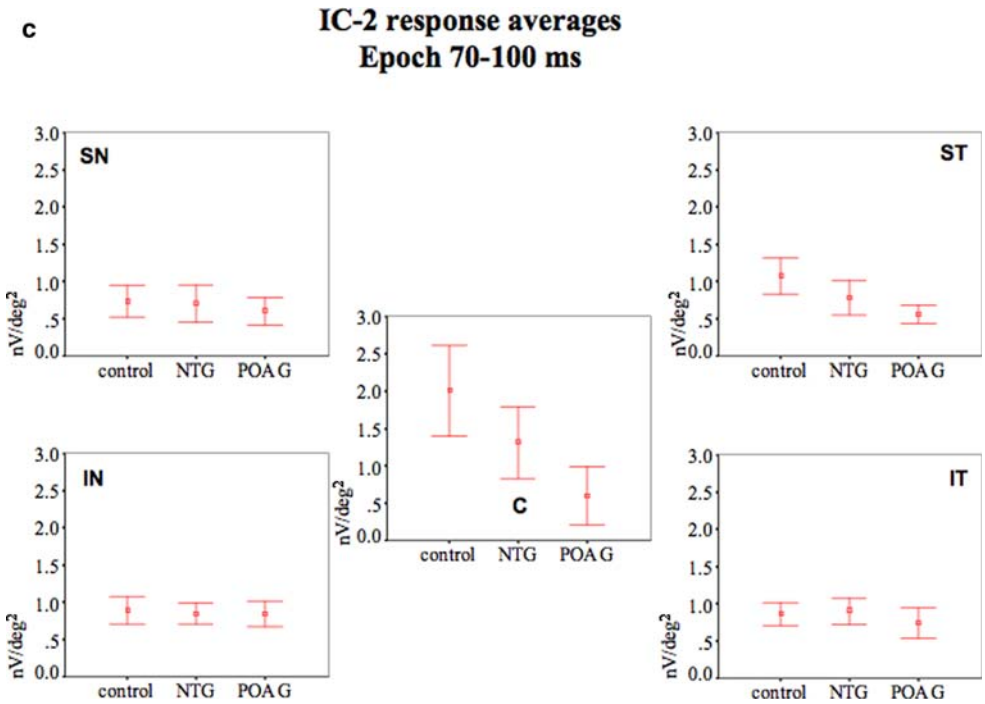

Fig. 5 continued

Discussion

In this study, significant changes were observed in the IC-1, where both NTG and POAG patients differed from controls in the response averages of the superior quadrants, and POAG patients also differed from controls in the centre. The most sensitive parameter was the IC-1 of the superior temporal quadrant where 80% of the NTG patients and 75% of the POAG patients were correctly classified as abnormal while 80% of the

Table 1 For the IC-1 and for each response average, Table 1 lists how the three groups: NTG, POAG and Control, compared to one another. Significant differences are highlighted in bold (multivariate ANOVA, Sidak)

Quadrants	Groups	*P*-value
superior-temporal	controls-NTG	**0.001**
	Controls-POAG	**0.000**
	NTG-POAG	0.992
superior-nasal	controls-NTG	**0.016**
	controls-POAG	**0.000**
	NTG-POAG	0.302
inferior-nasal	controls-NTG	0.661
	controls-POAG	0.052
	NTG-POAG	0.382
inferior-temporal	controls-NTG	1.000
	controls-POAG	0.417
	NTG-POAG	0.426
centre	controls-NTG	0.443
	controls-POAG	**0.003**
	NTG-POAG	0.103

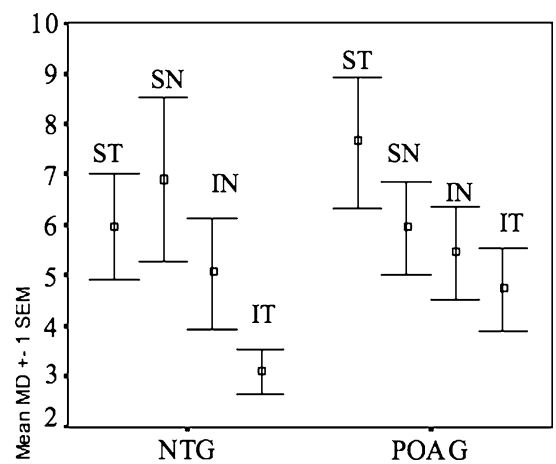

Fig. 6 shows the distribution of the mean defect for each of the visual field quadrants. The error bars depict ±1 standard error of the mean. While on average the MD was higher in the superior fields, it did not differ significantly between quadrants

Table 2 The ability of the IC-1to differentiate beween NTG, POAG and Control is shown for each response average. (a) depicts information on the area under the ROC curve with the corresponding *P* value when POAG and NTG are compared to the control group. (b) informs about sensitivity and specificity for the different response averages using given cutoff values

		ST	SN	IN	IT	Central
(a)						
POAG	Area	0.81	0.81	0.70	0.65	0.78
	P-value	0.00	0.00	0.03	0.09	0.00
NTG	Area	0.79	0.75	0.58	0.50	0.61
	P-value	0.00	0.01	0.36	0.97	0.21
(b)						
Cutoff value in nV/deg^2		2.50	2.40	2.30	1.40	3.40
% classified abnormal	POAG	75	75	65	30	55
	NTG	80	75	45	25	15
% Classified normal	control	80	85	80	80	85

control subjects were correctly classified as normal when a cutoff value of 2.5 nV/deg^2 was used. The DC and the IC-2 did not differ significantly between the groups. These results compare well to a study by Fortune et al. [25] who also found the induced component to be most sensitive when a one flash mfERG was applied, allowing glaucoma subjects to be identified with a sensitivity of 75% when a cutoff value of 2.75 nV/deg^2 was used.

In a mfERG with one global flash, Chu et al. [28] also showed an overlap of the DC but separated IC between glaucoma patients and a control group when, as in the present study, focal flashes of high luminance difference were used. Recording the response to various luminance differences between the DC and the IC (which remained at a stable luminance) of a one flash mfERG they were able to calculate an adaptive index that reflects the tendency of the DC to saturate at higher luminance differences and that also reflects nonlinear contributions to the DC. This saturation was less obvious in glaucoma, possibly due to reduced amplitudes at mid luminance difference levels. This adaptive index of the DC had a very high sensitivity of 93% with a specificity of 95%. This is higher, than the sensitivity found in the present study where, when all five response averages of the IC-1 were taken into consideration, 90% of the NTG patients and 85% of the POAG patients were correctly classified as abnormal while 80% of the

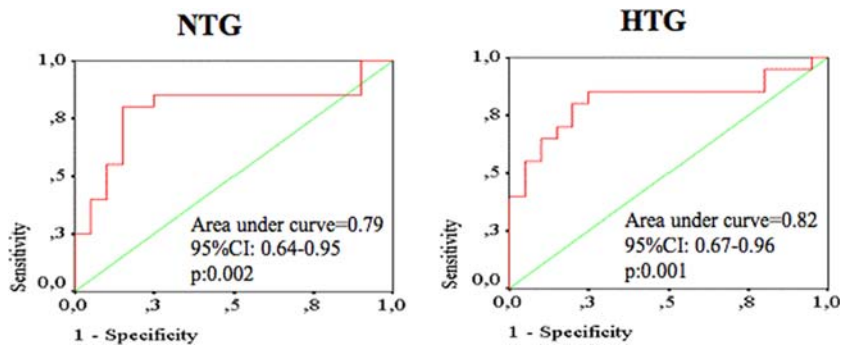

Fig. 7 Figure 7 depicts the receiver operating characteristics (ROC) curves for the IC-1 of the superior temporal quadrant for NTG patients (left) and POAG patients (right). If the values were aligned on the diagonal, this ability would be equal to chance. For a sensitivity and specificity of 100%, the ROC curve would follow the leftmost and the topmost margin of the graph. Thus, the area under the ROC curve is a measure of the ability of this parameter to differentiate between patients and controls. For NTG patients, the area under the ROC curve was 0.79 and for HTG it was 0.82, which is significantly better than chance ($P \leq 0.02$)

control subjects were correctly classified as normal. A longer follow period would be necessary to evaluate, what percentage of the 20% control subjects classified as abnormal will develop glaucoma. Thus at present, it is to early to tell, whether there is a 20% false alarm rate or whether the mfERG may be more sensitive to detect glaucomatous damage than either visual field defects or an increased cup-disc ratio, parameters which are currently required for the diagnosis of glaucoma.

The higher sensitivity and specificity found by Chu et al may also reflect more progressed glaucoma in their patients (mean MD: 7.79 (SD 5.76) [28], than in the present study where mean MD was 5.25 (SD 3.4) dB in the NTG group and 5.94 (SD 3.05) dB in the POAG group. A disadvantage of the adaptive index suggested by Chu et al. [28] is that it requires multiple mfERG recordings. In order to obtain this adaptive index patients underwent 4 mfERG recordings, each lasting 8 min [28] which is difficult to achieve in a clinical setting. This compares to one 10 min recording in the present study. From Fig. 4 in their paper [28] it seems that a small reduction in luminance difference of the focal flash to 1.42 cd*s/m^2 results in a clearer separation between both the DC and the IC of the one flash mfERG. This would be a promising approach in order to try and further increase sensitivity and specificity, using only a single recording eg. with the 2 flash mfERG.

In the present study, meaningful peak to peak measures were not feasible, as very small amplitudes with broad peaks were seen in quite a few mfERGs recorded. Therefore we chose the scalar product measure in order to objectively analyze each mfERG. The relevant findings of the present study are based on the scalar product measure, which reflects changes in amplitude as well as in latency. Fortune et al reported an amplitude reduction of the induced component in the one flash mfERG [25]. Thus, from this and from our observation of very small amplitudes, it is reasonable that our results also reflect reduced amplitudes. On the other hand, it seems likely, that latencies would also be affected to some extend, as they have previously been found to be slightly increased in the linear and nonlinear [9, 10] components of the mfERG without a global flash in glaucoma patients

In the no global flash-mfERG response of POAG patients small but robust changes have been reported [7–10]. Even though Fig. 5a shows a tendency for a reduced DC response in POAG, changes observed in the DC of the 2 flash mfERG did not approach significance level in either the NTG or POAG patients. The DC of the flash mfERG reflects different adaptive mechanisms across the retina that are not present in the conventional high contrast noflash mfERG [28]. This may be a result of the interdependence between the focal flash and the global flashes, in particular the dependence of the DC on the global flash (see following discussion).

Studies using one global flash in the mfERG stimulus sequence suggest that the luminance parameters used in our study (200 cd/m^2) appear to be among the stimulus settings that produce the largest IC- responses as well as good DC-responses. Shimada et al studied the one global flash mfERG response to various luminance conditions, ranging between 12.75 cd/m^2 and 800 cd/m^2. The luminance conditions were independently changed for the global flash and the focal flash [31]. With increasing luminance intensity of the global flash, the inter-individual variability was reduced. At the same time, the DC became sequentially smaller and its implicit time shorter. The IC-response was largest at a global flash intensity between 100–200 cd/m^2. For very dim focal flashes, the mfERG DC- and IC- response were below noise level. With increasing luminance of the focal flashes up to 200 cd/m^2, the IC-response increased, thereafter the amplitudes and latencies of the IC decreased [31]. Increasing the luminance and contrast conditions of the focal flash in a mfERG stimulation with one global flash in the stimulus sequence showed an increasing reduction in the IC-response amplitude of glaucoma patients when compared to a control group. In contrast, the response to the focal flash, the DC, differed most between glaucoma and control subjects at a mid luminance difference [28].

It is interesting to note that in the one global flash mfERG, not only do adaptive effects of the focal m-sequence stimulus influence the

IC- response, but the global flashes also influence the response to the focal flash [31]. This also holds true for stimuli with 3 global flashes, where the response to the focal flash is greatly altered [24]. These nonlinear contributions, have been reported to be much larger in the IC than in the DC. Of the nonlinear contributions to the mfERG, the optic nerve head component (ONHC) which has been attributed to the nerve fiber layer [11–16] is reflected in a large nasotemporal asymmetry of the mfERG response that may be diminished in glaucoma [15, 17]. Indeed, the IC has been shown to contain a large nasotemporal asymmetry, while this is only slightly present in the focal flash response [24, 25, 29–31]. These adaptive mechanisms are generally attributed to the inner retina [24, 25, 29, 30], suggesting that a global flash paradigm lends itself to the diagnosis of glaucoma.

In the present study however, even though the trace arrays of the stimulus show a marked nasotemporal asymmetry, this did not differ between the groups. The differences observed were concentrated on the upper hemifield. Nonetheless, we did not find a significant difference in the distribution of the mean defect of the different quadrants of the visual fields in either NTG or POAG patients that might explain this finding. This is in agreement with previous studies that did not find mfERG changes co-localized to visual field defects, either for the no global flash mfERG [19, 22] or for the pattern mfERG [32].

In conclusion, our results support previous findings, that interposing bright global flashes into the stimulation sequence, increases the sensitivity of the mfERG to detect retinal dysfunction in glaucoma [24, 25, 28]. While the second induced component of a 3 global flash mfERG had a 50% sensitivity to detect glaucomatous damage [24], this was increased to 75% with use of a single global flash mfERG (Area under ROC curve:0.88) [25]. The 2 global flash stimulus applied here, showed a comparable ability to differentiate POAG patients from control subjects when the first induced component in the superior temporal quadrant was analysed (Area under ROC curve: NTG: 0.79; POAG: 0.82). When all five response averages of the IC-1 were taken into consideration, 90% of the NTG patients and 85% of the POAG patients were correctly classified as abnormal while 80% of the control subjects were correctly classified as normal. Thus, a further, new finding of this study is, that this IC-1 had a similar ability to separate POAG, as well as NTG patients from the control group.

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